



# **Product Integrity Toxicological Evaluation Guideline**

## **Cigarette Products**

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## 1 Organization and Application of these Guidelines

A toxicological evaluation serves as the mechanism for providing guidance regarding the suitability for use of product components, packaging or manufacturing materials, processes, integrated technologies and integrated product designs. The Product Integrity Toxicological Evaluation Guidelines describe the basic approaches used in this evaluation. The guideline structure includes an over-arching decision making flow framework and the associated platform-specific guideline documents.

Altria Client Services - Product Integrity Toxicological Evaluation Guideline - Cigarette Products, applies to the evaluation of cigarette products. The Federal Cigarette Labeling and Advertising Act (FCLAA), 15 U.S.C. §1332(1)(A) and (B) defines a cigarette as "any roll of tobacco wrapped in paper or in any substance not containing tobacco . . . [and] any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette. . . ."

This document has two appendices which act as supplemental information to this guideline and may be revised independent of this guideline. Appendix A includes terminology definitions. Appendix B details chemical and biological assays that are available for use in the evaluation, including background regarding the relevancy of the assay for use with cigarettes. Additional procedures and process steps used as part of the evaluation are described in various Product Integrity guidance and Quality Management System documents.

## 2 Purpose of the Evaluation

“There is no safe cigarette. Philip Morris USA agrees with the overwhelming medical and scientific consensus that cigarette smoking causes lung cancer, heart disease, emphysema and other serious diseases in smokers. Smokers are far more likely to develop such serious diseases than non smokers.” (Philip Morris USA, 2008). Altria and its company Philip Morris USA are dedicated to assuring that none of its current or future products add to the existing reported health risks associated with cigarette smoking. We also support the spirit of the regulatory principles described by The Institute of Medicine (IOM), which include the use of appropriate toxicological testing methods to assess the use of ingredients in tobacco products (Institute of Medicine, 2001).

IOM Principle 8: “All added ingredients in tobacco products, including those already on the market, should be reported to the agency and be subject to a comprehensive toxicological review.”

The purpose of the toxicological evaluation is therefore to provide a basis for assessing whether the potential for product changes or new designs increase the inherent toxicity of smoke using established non-clinical toxicology testing methods. The constituents in

tobacco smoke are known to have numerous chemically and biologically significant effects and the long-term human health effects of many of these are not known completely. It is possible however to use chemical and biological tests to make assessments, that when viewed in a weight of evidence approach, gives reasonable assurance that the change will not increase the human health risk beyond that currently recognized.

### 3 Evaluation Rationale

The toxicologic evaluation is intended to provide a scientifically based assessment, such that use or implementation of a product component, packaging or manufacturing material, process, integrated technology or integrated product design can be avoided if such use or implementation is considered to increase the inherent adverse health effects associated with cigarette smoke. This guideline incorporates basic principles and science based on currently available information; however they can be revised when substantial changes are necessary.

Presently there are no established criteria or methodologies that encompass the expected variability of human smoke exposure, nor are there developed biological test models that specifically predict the range of health effects attributable to smoke. Because of these limitations, chemistry and/or surrogate non-clinical biological testing models have been developed using standardized machine smoking conditions for test substance generation. While this type of testing introduces some uncertainty regarding precise application of the results to the range of human smoke exposure situations, it does provide a stable basis for comparative testing purposes (*i.e.*, new design *vs.* old design, with ingredient *vs.* without ingredient). It is recognized that biological testing using *in vitro* or *in vivo* model systems also assumes some uncertainty for application to humans. It is therefore incumbent on the reviewer to use sound scientific judgment when interpreting the data used for a toxicologic evaluation.

This document, and the overarching decision making framework<sup>1</sup> are intended as guidance only, and do not establish rules. The guidance represents sound and up-to-date approaches, but assessments may be conducted differently than outlined here for a number of reasons. Novel cigarette product configurations may require unique evaluation approaches. Additional documentation will be included in the Product Integrity files describing exceptions to the routine evaluation procedure, as well as the justification for the exception.

Certain items that are not necessarily intended to be introduced into the market (*e.g.*, machine trials or analytical test models) are not necessarily subject to evaluation. However, items intended for use in the manufacturing of marketed products or a product intended for human consumption through subjective testing, are subject to an evaluation.

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<sup>1</sup> Product Integrity-Toxicological Evaluation Framework Overview

## 4 Weight of Evidence / Scientific Judgment

Since most evaluations will utilize data obtained from multiple sources of both chemical and biological relevance, the toxicological evaluation will consider relevant available data including the scientific strength of the results and the appropriateness of the testing methodologies. The weight of evidence approach where a single integrative decision is made after assessing all of the individual lines of evidence, is consistent with the approach incorporated into other health assessment guidelines including the US Environmental Protection Agency (EPA) Guidelines for Carcinogen Risk Assessment (EPA, 2005).

A critical element of the evaluation procedure is the application of sound scientific judgment based on knowledge of the variability and predictive power of the assay, as well as the variability of smoke and its inherent toxic characteristics. The evaluation procedure generally incorporates control cigarette designs which will elicit a biological response themselves. When considering the impact of any test model on the toxic potential of smoke, it is important to recognize this inherent baseline smoke toxicity.

The evaluation procedure is an iterative process. Initial views, conclusions and approaches may change from time to time as new information is incorporated into the evaluation procedure. Generally, no single factor (*i.e.*, report in the literature, endpoint or assay result) is unduly weighted, and the factors are not scored mechanically by adding pluses and minuses; they are judged holistically. These factors are taken into account throughout the evaluation with the goal of producing an objective appraisal of the available data. The weight of evidence approach addresses not only possible effects of the chemical or design, but also the conditions under which such effects may be expressed. Weight of evidence relies upon the expert judgment of a properly trained and experienced reviewer to evaluate the data and formulate rational conclusions. The entire range of information developed in the evaluation is reviewed to arrive at a decision. Decisions are drawn from the weight of evidence evaluations based on combined strength and coherence of inferences drawn from the available information.

## 5 Evaluation Fundamentals

### 5.1 Collecting Data

Since the toxicological evaluation procedure is based on a tiered approach these guidelines do not suggest that every piece of data covered here will necessarily be needed or available for evaluation. The level of detail is a matter of scientific judgement and discretion using the decision making framework and this guideline. Based on the various scientific and regulatory principles, considerations, and recommendations, as well as current toxicological knowledge, a core battery of work has been established for potential use in toxicological evaluations including: review of history of use and GRAS status, review of current scientific literature, analysis of potential chemicals generated by volatilization or pyrolysis, chemical analysis for mainstream smoke constituents, genotoxicity assays in bacterial and mammalian cells, and rodent smoke inhalation studies.

The assays that may be used to collect data are described in appendix B of this document.

### 5.2 Evaluating data

#### 5.2.1 Theoretical Exposure Concern Levels

The tiered concern level approach for dietary ingredient exposure has been used by the US Food and Drug Administration (FDA) in *Office of Food Additive Safety Redbook 2000: Toxicological Principles for the Safety Assessment of Food Ingredients* (FDA, 2000). Under the FDA procedure, Structure Category A materials are relatively toxicologically inactive structures whereas Structure Category C materials contain chemical structures with biologically active parts. Three categories of exposure are also defined. Based on the combination of Structure Category and exposure level, a Concern Level for dietary ingredients can be assigned for evaluation using recommended toxicity tests ranging from short-term *in vitro* genotoxicity tests to *in vivo* chronic and carcinogenicity assays.

Although the procedure described by the FDA is related to dietary exposure, the concept for evaluation using segregation of subject chemicals by structure and anticipated exposure level into Concern Levels is considered useful for the toxicologic evaluation of smoking products and their components. Since many of the product components evaluated by Product Integrity are derived from chemical mixtures and the potential for burning may exist, exposure levels and testing strategies designed for FDA Structure Category C, considered to be the most conservative situation for evaluation, are considered appropriate.

To convert dietary ingredient exposure Concern Levels into Concern Levels for potential exposures via smoking products, an assumption using 50 kg body weight and exposure to

2 packs of cigarettes per day was made (Waingrow *et al.*, 1968). The conversion and the resulting Concern Levels for theoretical exposure to materials used to manufacture cigarette products is shown in Table 1.

**Table 1: FDA Dietary Exposure Levels Converted to Equivalent Cigarette Product Exposure**

<b>Concern Level</b>	<b><u>Dietary Exposure (ug/kg-bw/day)</u></b>	<b><u>Assume 50 kg bw (ug/day)</u></b>	<b><u>Assume 40 cigarettes smoked /day Equivalent Cigarette Product exposure (ug/cig)</u></b>
<b>I</b>	<0.62	<31	<0.78
<b>II</b>	0.62 -12.5	31 - 625	0.78 -15.6
<b>III</b>	>12.5	>625	>15.6

A review of the literature on chemical transfer in cigarette smoke indicated that the range of measured transfer was 0.6 % to 23 % with an average of about 18% (VonHolt, 1999). To further characterize the level of an ingredient in a cigarette which corresponds to the concern levels, the following calculations and resulting cigarette concentrations given in PPM are shown in Table 2. For an individual ingredient this concentration is considered when determining testing/data collection requirements.

**Table 2: Equivalent Cigarette Product Exposure converted to Part Per Million Cigarette Concentration**

<b>Concern Level</b>	<b><u>Cigarette Ingredient Level<sup>a</sup> (ppm)</u></b>	<b><u>Possible Ingredient Exposure Level (ppm)</u></b>	<b><u>ppm- rounded</u></b>
<b>I</b>	<0.98	<4.9	<5
<b>II</b>	0.98 - 19.5	4.9 - 97.5	5 -100
<b>III</b>	>19.5	>97.5	>100

<sup>a</sup>Assumes 0.8g tobacco per cigarette (0.78ug/cig X 1cigarette/0.8g = 0.98 ug/g tobacco or ppm)

<sup>b</sup>Assumes 20% transfer to smoke (0.98/0.20 = 4.9 ug/cig or ppm)

Regulatory and authoritative bodies have increasingly concluded that there is an apparent safe exposure level for certain chemicals, and continue to establish chemical exposure thresholds below which they consider exposure as toxicologically insignificant. For food packaging materials that may migrate into food, the FDA evaluated over 300 carcinogens in order to estimate levels that would represent risks to be sufficiently small enough to be unworthy of any further regulatory consideration. It has been concluded that this risk level is equivalent to about 0.5 ppb in food (1.5 ug/person/day). (21CFR170.39) This exposure is equal to about 0.05 ug/cigt based on the following assumptions: 40 cigarettes

per day, 0.8 g cut filler (tobacco), 100% transfer into smoke and 100% absorption in lung.

The FDA also addressed the issue of impurities as constituents of food in 1982 by recognizing that chemicals have impurities and decisions concerning the safety of the impurities must take into consideration the concept of threshold of regulation. For impurities below a projected dietary level of approximately 1 ppb the concept of negligible or *de minimis* risk was considered appropriate. In 1996, the Congress passed the *Food Quality Protection Act of 1996*. This Act amended FIFRA and FFDCA setting forth a new safety standard in 408(b)(2)(A)(ii). The standard is one of “reasonable certainty of no harm” from exposure. Although this law did not set forth specific standard for “reasonable certainty of no harm,” the premise allowed for a level of very small risk that is accepted by society. In 1986, California approved an initiative to address growing concerns about exposure to toxic chemicals. The initiative became *The Safe Drinking Water and Toxic Enforcement Act of 1986*, better known as Proposition 65. The law required manufacturers to warn, through labeling, if their products contain carcinogenic chemicals. The law recognized that there may be small levels of chemicals present in products that do not present a significant risk to consumers and therefore defined the “no significant risk level” as the level which is calculated to result in not more than one excess case of cancer in 100,000 individuals exposed over a 70-year lifetime.

The most conservative approach is that of the FDA where 1.5 µg/person/day in food as a result of migration from packaging is considered a level of *de minimis* risk for cancer.

Generally, for purposes of the toxicologic evaluations conducted using this Product Integrity guideline, chemical exposures which can reasonably be expected to be below 1.5 µg/person/day (0.05 ug/cigt) will be considered below the threshold of concern; however for agents of particular toxicity concern this threshold may not apply.

### 5.3 Toxicity Considerations

Certain biological topics may have importance when conducting toxicologic evaluations with cigarette smoke. Four such areas are discussed below. However, exclusion of other chemical and biological endpoints used for the toxicologic evaluation does not imply that they will not be used in the overall weight of evidence approach, and these may be considered on a case-by-case basis as necessary.

#### 5.3.1 Genotoxicity

Genotoxicity studies are designed to evaluate a specific end-point that is considered to be suggestive of the potential to cause some form of genetic change in humans. However, the underlying information on the potential genotoxicity of chemicals is complex and often difficult to interpret and the relevance of observations in bacteria used for *in vitro* testing to human exposure continues to be debatable.

A weight of evidence approach will utilize considerations such as use level, likelihood to be delivered to the adult smoker, indigenous presence of the chemical in tobacco or smoke, and likelihood that risk of the product itself would be lessened if the chemical were not used.

### 5.3.2 *Carcinogenicity*

Carcinogenicity studies are complex and difficult to interpret because the routes of exposure and/or dosages may not be relevant to humans. Furthermore, some scientific evaluations of the mechanisms underlying the carcinogenic response in animals have determined these mechanisms are not relevant to humans. Nonetheless, various bodies of experts (*e.g.*, EPA, International Agency for Research on Cancer (IARC), National Institute for Occupational Safety & Health (NIOSH), National Toxicology Program (NTP)) have given considerable attention to the evaluation of the carcinogenic potential of many chemicals in humans based upon the results from animal studies. An analysis of the various agencies that provide information of carcinogenic hazards suggests the IARC and NTP provide the most comprehensive listing of chemicals, provide detailed information regarding the supporting information, and have attempted to incorporate 'likelihood' qualifiers such as known, possible, probable, sufficient, limited, and reasonably anticipated.

Comparison of carcinogens identified on the IARC and NTP lists with the FDA's Everything Added to Food in the US list, indicates that there are cases of overlap. For certain chemicals specific use conditions and/or residual limitations may apply, while for others use is limited only by current manufacturing practices. Additionally, natural substances commonly used in foods may contain individual chemical entities which have displayed carcinogenic potential. Thus, for some chemicals with carcinogenic activity there appears to be some level of accepted risk.

Assessment principles and practices for carcinogens are emerging <sup>1</sup>, and can serve as models for gauging the impact of adding a chemical listed as a carcinogen by IARC or NTP to a cigarette product. A weight of evidence approach will utilize considerations such as relevance of the toxicology information to human exposure, use level, likelihood to be delivered to the adult smoker, indigenous presence of the chemical in tobacco or smoke, and likelihood that risk of the cigarette product itself would be changed if the chemical were not used.

### 5.3.3 *Reproductive and Developmental Toxicants*

Various bodies of experts have published assessments of chemical reproductive and developmental toxicity including California Environmental Protection Agency (CalEPA) Office of Environmental Health Hazard Assessment (OEHHA) and the National

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<sup>1</sup> Practices such as the EPA Guidelines for Carcinogen Risk Assessment (EPA, 2005)

Toxicology Program (NTP) – Center for the Evaluation of Risks to Human Reproduction (CERHR).

A weight of evidence approach will utilize considerations such as use level, likelihood to be delivered to the adult smoker, indigenous presence of the chemical in tobacco or smoke, and likelihood that risk of use of the product itself would be lessened if the chemical were not used.

#### 5.3.4 *Allergens*

Some individuals may become immunologically sensitized to certain chemicals in a manner that may lead to severe life-threatening allergic reactions upon subsequent exposure to that chemical. To be considered in this category, the chemical should have documented cases of life-threatening allergic reactions reported in a credible scientific publication, or several independent reports of these allergic reactions. In the food, cosmetic, and pharmaceutical industries, it is common to label products containing a “recognized” allergen so that persons allergic to that chemical can avoid those products.

Chemicals which are known human allergens capable of eliciting a life-threatening reaction (*e.g.*, anaphylactic shock or asthmatic attack) after administration by a relevant route, and are anticipated to be available intact to the smoker, will be considered not acceptable in product components, or the package will be labeled indicating the presence of the chemical.

Chemicals which are known human allergens capable of eliciting a dermal, oral or other hypersensitivity reaction after administration by a relevant route will not be used in filters unless it can be determined that the chemical is not allergenic under the conditions of use.

#### 5.3.5 *Decision Making*

As described in the Product Integrity Toxicological Evaluation Decision Making Framework Overview and associated flow chart, the amount of data collected and testing needed to make a decision will depend on such things as the potential exposure, the history of use, the potential for the material to be burned, current use status (new vs. currently used) and the use level. Most toxicologic evaluations will utilize data obtained from multiple sources.

The toxic potential of cigarette products has been established using several biological and chemical assays. The assays suggested in this guideline generally incorporate control groups which will frequently elicit a biological response. It is important to recognize that any relative comparisons between test and control designs must consider the inherent toxicity as evidenced by the array of background changes normally seen with smoke exposure studies, as well as the variability frequently observed with chemical and biological testing of smoke. Uncertainty and variability of the assay methods should also be considered.

From time-to-time documents such as Ingredient Reviews, Part-type Summary Papers, or Scientific Data Summaries will be prepared to summarize the current extent of knowledge regarding product components, packaging or manufacturing materials, processes or product designs. These scientific review documents are intended to include relevant toxicological information on the specific topic. They are not necessarily intended to apply to any specific toxicologic evaluation, but rather serve as a source of information applicable to multiple evaluations and toxicological questions.

The evaluation will therefore consider and weigh the relevant available data based upon the scientific strength of the results and the appropriateness of the testing methodologies. This type of weight of evidence approach, where a single integrative decision is made after a collective evaluation of pertinent information is considered, is consistent with the approach incorporated into other health assessment guidelines including the EPA Guidelines for Carcinogen Risk Assessment (EPA, 2005). Judgment about the weight of evidence involves consideration of the quality and consistency of responses induced by the item in question.

Only those individuals with adequate training and/or experience (*i.e.*, credentialed according to the current credentialing guidelines for Product Integrity) will be allowed to make decisions regarding the evaluation.

## 6 Guideline Evolution

We consider the evaluation approach and current assays used in our guidelines to be consistent with the state of the art for cigarette products and consistent with approaches used for other consumer products. However, we will continue to evolve the evaluation procedure by developing and incorporating newer methodologies and approaches that we feel are relevant to the evaluation process. With this perspective, it is expected that the methods and approaches used will vary from time to time as we continue to improve our evaluation procedure.

## 7 Revision History

Revision #	Date	Reason for Revision
00	09/02/1999	Original
01	DRAFT	Document changes in the approach for this evaluation, and putting it into current Quality System format

## 8 References

EPA. (2005) EPA Guidelines for Carcinogen Risk Assessment. US Environmental Protection Agency, Washington, DC. Risk Assessment Forum.

Institute of Medicine. (2001) *Clearing the smoke: Assessing the science base for tobacco harm reduction*. Stratton, K, Shetty, P., Wallace, R., and Bondurant, S. National Academy of Sciences, Washington, DC.

Office of Food Additive Safety Redbook 2000. (2000) *Toxicological Principles of the Safety Assessment of Food Ingredients*. Updated October 2001 & November 2003. US Food and Drug Administration, Washington DC.

Philip Morris USA. (2008). *Smoking and Health Issues: Smoking and Disease in Smokers*. Retrieved 4/17/08 from [http://www.philipmorris.com/en/cms/products/cigarettes/health\\_issues/cigarette\\_smoking\\_and\\_disease/default.aspx](http://www.philipmorris.com/en/cms/products/cigarettes/health_issues/cigarette_smoking_and_disease/default.aspx)

Von Holt, K. (2-24-1999) 'Ingredient Transfer into Mainstream Smoke'. Internal Report (Bates # 2064259215-2064259234)

Waingrow, S, Horn, D., and Ikard, FF. (1968) Dosage patterns of cigarette smoking in American Adults. *American Journal of Public Health*. 58: 54-69.

## Appendix A -Definitions

*Biologically Significant Effect:* A numerical or qualitative change (increase or decrease) in non-clinical and/or clinical indicators relative to a specified reference that may or may not show statistical significance in a scientifically valid and specified statistical test. The biologically relevant change is judged by an expert or a group of experts as having biological relevance after taking the variations of the analytical procedures and the biological variation of the test system(s) and historical data into account. Biologically relevant changes are distinguished from biological changes that may be statistically significant but have no biological relevance in a toxicological assessment. Biological relevance and biological significance are expert judgments.

*Chemical:* Identified material listed in a disclosure or MSDS for a product component or discovered by analytical techniques.

*Cigarette:* The Federal Cigarette Labeling and Advertising Act (FCLAA), 15 U.S.C. §1332(1)(A) and (B) defines a cigarette as "any roll of tobacco wrapped in paper or in any substance not containing tobacco . . . [and] any roll of tobacco wrapped in any substance containing tobacco which, because of its appearance, the type of tobacco used in the filler, or its packaging and labeling, is likely to be offered to, or purchased by, consumers as a cigarette. . . ."

*Constituents:* Substances that make up cigarette smoke.

*Integrated Product Design:* The combination of the purchased and manufactured components that are used to produce a product.

*Manufacturing Materials:* Those items which are used to facilitate the manufacturing process, but are not intended to become a part of a product. The term "manufacturing materials" is intended to include those operating supplies that are needed to support/facilitate production at manufacturing facilities, and any repair parts (physical parts of the production process) that may come in contact with a product, its packaging or labeling.

*Packaging Material:* Those items used to physically contain a finished product. They include those items which may be in direct contact with a product, but are not intended to become a part of a product. Conceptually these items would include the various layers of product containment (*e.g.*, inner foil, pack material, poly wrap, carton material, case material as well as inks and associated adhesives).

*Part-type:* A term used to identify particular parts of a product such as the filter, cigarette paper, tipping paper, flavors, etc.

*Part-type Summary Document:* A summary of PM USA research and knowledge about a particular product component or part-type.

*Product Component:* Product components comprise those materials which are directly added to a product for a specific functional purpose (excluding tobacco). The term Product Component is intended to include the terms “additives, ingredients and non-tobacco components” which are sometimes used for regulatory disclosure and communication purposes. A product component can be a pure chemical or a mixture of chemicals.

*Scientific Data Summary: (SDS)* A summary of PM USA research and knowledge about a particular product.

*Scientific Review Document:* A summary of relevant information about a product component, packaging or manufacturing material, process or product that could include published and unpublished internal and external research and knowledge. (Could take several forms, for example: Ingredient Review, Part Type Summary Document, or Scientific Data Summary)

*Technology:* The method and material used to achieve a commercial or industrial objective.